Negative symptoms in first-episode psychosis: clinical correlates and one-year follow-up outcomes in London Early Intervention Services

Aikaterini Rammou[a,b], Helen L. Fisher[a], Sonia Johnson [c,d], Barnaby Major[e,f], Nikola Rahaman[g], Nick Chamberlain-Kent[h], James M Stone[a,I,*]

[a] Institute of Psychiatry, Psychology & Neuroscience, King's College London, London, UK

[b] School of Psychology, University of Sussex, Brighton, UK, e-mail address: ar353@sussex.ac.uk

[c] Division of Psychiatry, University College London, London, UK.

[d] Camden and Islington NHS Foundation Trust, London, UK.

[e] EQUIP, Hackney, East London NHS Foundation Trust, London, UK.

[f] Herefordshire Early Intervention Service, 2gether NHS Foundation Trust, Herefordshire, UK.

[g] Kensington, Chelsea, Westminster and Brent Early Intervention Service, Central & North West London NHS Foundation Trust, London, UK.

[h] Wandsworth Early Intervention Service, South West London & St Georges' Mental Health NHS Trust, London, UK.

[i] South London and Maudsley NHS Trust, UK.

***Corresponding author:** Room L2.06, PO89, Centre for Neuroimaging Sciences, Institute of Psychiatry, Psychology & Neuroscience, 16 De Crespigny Park, London SE5 8AF, UK.

E-mail address: james.m.stone@kcl.ac.uk; Tel no: 02032283053

Abstract

Negative symptoms remain an unmet clinical need, and yet have been generally associated with poor outcome in patients with schizophrenia. The association of negative symptoms with clinical features at presentation and with outcomes at 1 year were examined in a sample of first-episode psychosis patients in London (UK). Clinical data were utilized from five London Early Intervention Services included in the MiData audit database. The sample comprised 484 first-episode psychosis patients with complete Positive and Negative Syndrome Scale data at baseline and 1-year follow-up. Multiple imputation (N = 50) was conducted to account for missing follow-up data. Baseline negative symptoms were associated with male gender (B = -1.63, p <. 05), younger age of onset (B = -.15, p <. 05), a higher level of impairment on the Global Assessment of Functioning (disability) scale at baseline (B = -.19, p <. 010), an absence of reported substance misuse prior to baseline assessment (B = -3.05, p <. 001), and unemployment at baseline (B = -.93, p <. 01). At 1-year follow-up, negative symptoms at presentation were associated with worse Global Assessment of Functioning symptom (B = -.28, p <.01) and disability (B = -.27, p <. 05) scales, and with hospital admission (OR= 1.06, p <.01). Negative symptoms at presentation to Early Intervention Services were associated with poorer outcomes one year later. Future research is required to better understand the aetiology and trajectories of negative symptoms in early psychosis and propose novel targeted early interventions.

Key words: early intervention; first-episode psychosis; negative symptoms; psychosis; schizophrenia

1. Introduction

Negative symptoms (NS) remain an unmet therapeutic need for people suffering from psychosis (Chue and Lalonde, 2014; Kirkpatrick, 2014; Millan et al., 2014). In first-episode psychosis (FEP) studies NS at onset have been linked with poor social functioning after the first year of treatment and at 2 and even 7 years after first presentation to services (Ayesa-Arriola et al., 2013; Best et al., 2014; Milev et al., 2005). In a 3-year longitudinal study of first-episode non-affective psychosis, Ayesa-Arriola and colleagues (Ayesa-Arriola et al., 2013) also demonstrated that NS independently predicted impaired functioning at 1-year follow-up. Moreover, Best and colleagues (Best et al., 2014) indicated NS as the best symptomatic predictor of functioning both cross-sectionally and longitudinally in a FEP sample, in keeping with other early psychosis (Cacciotti-Saija et al., 2016) and mixed chronicity (Hunter and Barry, 2012; Rabinowitz et al., 2012) studies.

Research has also linked NS with symptomatic outcomes and recovery after a FEP. Among other variables, NS were reported as predictors of a continuous illness course at 5-year follow-up (Bertelsen et al., 2008) and were associated with a lower likelihood of achieving recovery (Gee et al., 2016; Novick et al., 2009; Schubert et al., 2015). Concerning the prognostic value of NS at onset, several studies have found that NS severity was associated with the likelihood of not achieving a clinical remission during one or two years of treatment (Díaz et al., 2013; Gaebel et al., 2014; Levine and Leucht, 2013; Üçok et al., 2011; Verma et al., 2012). Moreover, lower level of NS at baseline (Üçok et al., 2011) have been found to predict remission in other FEP studies. Marchesi and colleagues (Marchesi et al., 2015, 2014a) showed that NS at onset were linked to poor outcome in terms of remission at 16 years. Another FEP follow-up study using the Danish OPUS cohort indicated that lower severity of NS at baseline along with earlier age of diagnosis predicted better rates of recovery, defined as the combination of symptomatic and functional remission, at the 2- and at the 10-year follow-up assessment (Austin et al., 2013; Petersen et al., 2008).

Previous findings therefore suggest that high levels of NS have a debilitating effect on the early course of psychosis, despite the discrepancy of findings due to methodological variations across studies (Albert et al., 2011). However, NS have only been recently explored more extensively in the early course of psychosis, with only a few studies investigating their relationship with outcomes and baseline characteristics in FEP samples that included both affective and non-affective psychotic disorders. Moreover, there has been limited research investigating the impact of NS on outcomes of FEP patients being cared for by specialist services. Early Intervention Services (EIS) have been established across UK aiming to intervene early and effectively in young people experiencing FEP, following an assertive multidisciplinary outreach model, including pharmacological and psychosocial interventions (Fisher et al., 2008; Singh, 2010). Data utilized for the purposes of this naturalistic 1-year follow-up study were taken from five EIS in London, UK (Fisher et al., 2008).

Therefore, the aims of this study were to examine: (1) possible baseline socio-demographic and clinical correlates of NS at first presentation to EIS, and (2) the relationship between NS at baseline with clinical and functional outcomes at 1-year follow-up.

2. Material and Methods

2.1 *Setting*

This study was a naturalistic cohort of consecutive referrals to seven London EIS in the UK, assessed within one month of entry and followed up after one year. The teams were based in the following National Health Service (NHS) Mental Health Trusts in England: Camden and Islington (C&I EIS); South London and Maudsley (Lewisham EIS & STEP); East London and the City (EQUIP); Central and North West London (Brent and Kensington, Chelsea & Westminster EIS) and South West London and St. George's (ETHOS).

2.2 Participants

The patient inclusion criteria for EIS services were: (i) aged between 14 and 35 years old, (ii) presenting to the EIS for the first time with a psychotic episode lasting at least 7 days, and (iii) resident within the EIS catchment area (Fisher et al., 2008). Patients with psychotic symptoms as a result of acute drug intoxication were excluded.

2.3 MiData audit tool

Data were collected using the MiData audit tool, a standardized computerised assessment package of a minimum set of assessments used in routine clinical practice in EIS. This tool was developed by the London Early Intervention Research Network in 2004 in order to ensure consistent auditing of the EIS across London (see the original MiData paper for more details) (Fisher et al., 2008). Baseline measures were completed by clinicians based on their routine comprehensive assessments within 1 month of entry to the EIS and then 1 year later (follow-up). All clinicians were trained and were expected to reach at least 85% concordance with expert raters and other team members before being allowed to complete the measures on their patients (Kay et al., 1987).

2.4 Assessment measures

2.4.1 Socio-demographic information. Basic demographic data were obtained at baseline, including gender, age at onset of psychosis, employment status, and ethnicity based on the 2001 UK national census categories. Participants were assessed for the presence or absence of: (i) social support, with a categorization of ‘good’ (supportive and well-organized social environment, which benefits the patients’ recovery), ‘limited’ (existence of some level of social support, which does not cover all the needs of the patient) or ‘none’ (non-existent social networks); and (ii) family history of psychosis in a first-degree relative.

2.4.2. Clinical measures. At baseline, duration of untreated psychosis (DUP) was assessed with a revised version of the Nottingham Onset Schedule (Singh et al., 2005). DUP was defined as: the number of days between the appearance of the first positive psychotic symptom (hallucination, delusion or thought disorder) and the date that antipsychotic medication was initiated and thereafter taken for at least 75% of the subsequent month. Individuals were assessed on the following measures at entry to the service and after 1 year in contact with the service: the Positive and Negative Syndrome Scale (PANSS)[28] including positive (PANSS-P), negative (PANSS-N) and general (PANSS-G) subscales; the Global Assessment of Functioning Scale for symptoms (GAF-s) and disability (GAF-d) (Endicott et al., 1976); and the Combined Alcohol and Drug Use Scale (Drake and Wallach, 1989; Fisher et al., 2008). International Classification of Diseases 10th edition (ICD-10) (World Health Organization, 1993) diagnosis was recorded at 1-year follow-up and was extracted from clinical records and confirmed with EIS consultant psychiatrists. These were grouped into schizophrenia-spectrum disorders (ICD-10 codes F20-29), affective psychoses (F30.2, F31.2, F31.5, F32.3, F33.3 or F39), and other disorders (all other codes).

During the 1-year follow-up period, the occurrence of psychiatric admission to an in-patient ward, the use of a crisis or Home Treatment team (HTT), and the occurrence of any suicide attempts or of any violent incidents was determined from the clinical records. Adherence to treatment was ascertained using the treatment adherence subscale of the Service Engagement Scale (Tait et al., 2002), scored on a four-point Likert-type scale, with higher scores reflecting patients' greater levels of non-compliance.

Two new composite variables were created. Firstly, PANSS–D yielded presence of depression at baseline when patients had a score greater than 3 for all the following PANSS-G items: somatic concerns (G1), anxiety (G2), guilty feelings (G3) and depression (G6).(Kay and Sevy, 1990; Kjelby et al., 2011) This measure was created to ensure that the NS explored were not secondary to depression. Secondly, based on follow-up PANSS data, overall symptomatic Remission was defined as scores ≤ 3 on all of the following PANSS items: delusions (P1), unusual thought content (G9), hallucinations (P3), conceptual

disorganization (P2), mannerisms and posturing (G5), blunted affect (N1), social withdrawal (N4), and lack of spontaneity (N6). Overall symptomatic Remission was also calculated at baseline, using PANSS baseline data. Positive Symptom Remission was defined as scores ≤3 for the P1, P2, and P3 items at 1-year follow-up (Andreasen et al., 2005).

2.5 Preliminary data analysis

The MiData data freeze used was dated 11th of August 2014, and consisted of 1108 patients. For the purpose of this study, only patients with fully completed PANSS data at baseline were included in the sample (N = 516). In order to explore any possible systematic bias, baseline clinical and sociodemographic variables in patients with fully completed baseline PANSS data were compared to patients with missing PANSS data using chi-square and independent samples t-tests as appropriate (see Supplementary Material Appendix A). Patients with fully completed PANSS data at baseline (N = 516, M (SD) = (7.64) 17.80) had lower scores on PANSS-P than those with missing data (N = 592, M (SD) = (7.74) 20.66, t (593) = 3.10, p <.01). Moreover, there was a significant difference between availability of PANSS total scores in different ethnic groups (χ^2 (7) = 26.69, p < .001). In post-hoc chi-square analysis, compared to all other ethnicities, those of Asian ethnicity were more likely to have complete PANSS data and those with ethnicity recorded as "Black Other" were less likely to have complete PANSS data. No statistically significant differences were found regarding other variables (all p's >.05).

Normality and outliers testing was carried out for all continuous variables used in the analysis. Although Total Positive PANSS (PANSS-P), the Total Negative PANSS (PANSS-N) and the PANSS total were positively skewed, they were not transformed due to the large size of the sample and in order not to lose their clinical meaning. For the regressions, collinearity between independent variables was tested for with the variance inflation factor (VIF) (Field, 2009).

2.6 Missing data and multiple imputation

Based on Missing Values Analysis (see Supplementary Material Appendix B), none of the patients from Lewisham and STEP EIS that were initially in the dataset had completed PANSS at 1-year follow-up and consequently were excluded from the analysis. The remaining sample comprised 484 participants. Table 1 shows the rates of missing data for the variables used in this study. Little's missing completely at random (MCAR) test (Little and Rubin, 1991) for all the socio-demographic and clinical variables that were used for the main analyses of the study was not significant, suggesting that data were missing completely at random (χ^2 (1069) = 904.11, p = 1.00).

Missing values were imputed using Multiple Imputation (MI) creating 50 imputed data sets, with the SPSS Automatic method (see Supplementary Material Appendix C). Instead of using the totals for the PANSS subscales, all individual items were entered to enable creation of the composite variables of Remission and the PANSS-D factor. The number of imputations was similar to the highest percentage of missing cases.(White et al., 2011) The main analyses were conducted on the imputed datasets and the results were extracted from the pooled estimates.

2.7 Main analyses

Hierarchical linear regression was conducted in order to explore associations with socio-demographic or key baseline clinical variables and baseline NS, with PANSS-N being the dependent variable. To investigate the relationship of baseline PANSS-N with outcomes at 1-year, multiple linear regressions and binomial logistic regressions were carried out for continuous and categorical outcome variables respectively, using baseline PANSS-N as the predictor in each case. The outcome variables at 1-year follow-up were Remission, Positive Symptom Remission, GAF symptoms (GAF-s) and GAF disability (GAF-d), whether patients used Crisis teams, whether they were admitted to a psychiatric ward, whether they attempted suicide or whether they engaged in any violent incidents towards others.

An adjusted estimate for each of the regressions was then calculated to take into account previous reports of clinical and demographic associations with outcome by including ethnicity (van der Ven et al.,

2012; Veling, 2013), social support at baseline (Norman et al., 2012, 2005), family history of psychosis (Esterberg and Compton, 2012), gender (Galderisi et al., 2013; Tseliou et al., 2015), age at onset (Chang et al., 2012a; Malla, 2005), employment status at baseline (Abdel-Baki et al., 2013; Tandberg et al., 2012), DUP (Chang et al., 2012b; Fraguas et al., 2014; Jeppesen et al., 2008; Tang et al., 2014), clinical diagnosis at 1-year follow-up (Lyne et al., 2012; Singh, 2000), adherence to medication (Alvarez-Jimenez et al., 2012) and substance abuse or dependence 6 months prior to assessment (Tarricone et al., 2014) as covariates. In addition, PANSS-D, PANSS-P and Remission status at baseline were included as covariates in order to control for depression and severity of psychotic symptoms at baseline. Lastly, since the data were drawn from different EIS in different parts of London, team was also included as a covariate in the adjusted model. All analyses were carried out using SPSS version 22 (IBM).

2.8 Ethical Approval

Data collection by each EIS was conducted in accordance with local audit procedures, which do not require patient consent. Any information that could lead to patient identification was removed (Fisher et al., 2008). Multi-centre ethical approval was obtained from the Wandsworth Research Ethics Committee, which granted permission for secondary research use of the data for a specific set of research questions, including NS and clinical outcomes.

3. Results

3.1 Sample characteristics at baseline assessment

Socio-demographic and clinical characteristics of the sample (N = 484) are summarised in Table 2. Both pooled estimates from the 50 imputed datasets and the original dataset are presented. This sample comprised 315 males (61.5%) and the mean age of psychosis onset was 22.9 years (SD = 5.12).

3.2 Baseline Negative Symptoms and characteristics at presentation to EIS

An exploratory forced entry hierarchical linear regression analysis revealed a significant association between baseline PANSS-N score and gender, age of onset, substance use in the preceding 6 months, occupation status and GAF-d score (R^2 =.31, F (21, 462) = 12.75, p < .001; Table 3). Female participants had lower PANSS-N scores at baseline than males (p = .020); those with any substance use in the past 6 months before baseline assessment had lower PANSS-N than those that had not used (p <.001); participants that were employed or in education at baseline scored lower on PANSS-N than those who were unemployed (p = .014); those with more impaired functioning had higher NS (p < .001); and younger age of onset was also associated with higher PANSS-N scores (p = .035).

Post-hoc analysis of the relationship between PANSS-N at baseline and individual substance use including opioid, cannabinoid, alcohol, nicotine, cocaine and stimulant use in the model, revealed that only cannabinoid abuse or dependence was associated with lower PANSS-N scores (B = -2.17, B SE = .94, t = -2.39, 95% CI -4.01 – -.33, p =.021; Supplementary Materials, Table D1).

3.3 Baseline NS and clinical outcomes at 1-year follow-up

PANSS-N at baseline was significantly associated with worse symptoms (GAF-s; B = -.28, p =.007) and more impaired functioning (GAF-d; B = -.21, p = .01) at 1-year follow-up (Table 4). PANSS-N at baseline was also associated with patients being more likely to have been admitted to a psychiatric ward during 1-year follow-up, with one point increase in PANSS-N increasing the odds of being admitted during 1-year follow-up by 6%, (OR = 1.06, 95% CI 1.03 – 1.10, Wald statistic = 14.77, p =.001; Table 5). The mean (SD) PANSS-N of those who were admitted (N = 206) was 18.70 (9.47) compared to 14.99 (7.34) for those who were not admitted (N = 278). However, no significant associations were found between NS at baseline and Remission of symptoms at 1-year follow-up, nor with risk behaviors or use of HTT or Crisis teams during this period.

4. Discussion

4.1 Negative symptoms: baseline correlates

Participants with higher levels of baseline NS were much more likely to be male, in accordance with previous literature in both cross-sectional (Drake et al., 2016; Thorup et al., 2007) and follow-up FEP studies (Stone et al., 2014; Thorup et al., 2014). Thus, although earlier investigations of gender-specific patterns of negative psychopathology have been contradictory (Ochoa et al., 2012), most early psychosis studies are consistent with our findings (Köhler et al., 2009; Køster et al., 2008; Thorup et al., 2014, 2007; Willhite et al., 2008), including at-risk for psychosis research (Rietschel et al., 2015). A recent 1-year follow-through study by Gee and colleagues (Gee et al., 2016) reported that stable high NS during the first year of treatment were also predicted by male gender.

In the present study, severity of baseline NS was also related to a younger age of psychosis onset, which is consistent with most (Ballageer et al., 2005; Dominguez et al., 2010; Drake et al., 2016; Üçok and Ergül, 2014), but not all (Schultz et al., 1997), previous findings. It is noteworthy that a recent meta-analysis indicated that prominent NS at presentation for those under the age of 18 years of age should be considered as one of the core predictors for severe functional and clinical outcomes (Díaz-Caneja et al., 2015).

The present study suggests that patients with a higher level of NS had worse social and vocational functioning at baseline. This is in keeping with previous work in FEP patients by Best *et al.*(Best et al., 2014) who found that NS were related to functioning, both cross-sectionally and longitudinally. Previous research with mixed samples in terms of illness chronicity, have also supported NS as the most functionally impairing symptom in psychosis, predicting both baseline functioning and change in

functioning with illness progression (Ayesa-Arriola et al., 2013; Hunter and Barry, 2012; Rabinowitz et al., 2012). Poor premorbid functioning in those with prominent levels of NS at first presentation with psychosis could explain the poor social functioning found at baseline (Chang et al., 2016). Thus, patients with NS might have already suffered functional deterioration during the at-risk phase of psychosis (Corcoran et al., 2011; Kim et al., 2013; Meyer et al., 2014), since NS seem to have a more insidious onset and to emerge before positive symptoms, with the latter usually leading to contact with EIS (Hafner et al., 1993; Harvey et al., 2006).

We found that substance abuse or dependence in the 6-month period preceding entry to EIS was associated with lower levels of NS at presentation. Although there is a lack of FEP research on this relationship, existing studies are conflicting, with some being in agreement with the present result (Addington and Addington, 1998) and others not finding any differences in NS symptoms between substance users and non-users (Sevy et al., 2008).

In a post-hoc regression, only abuse of cannabinoids was a significant predictor for lower baseline NS levels, while accounting for other recent substance abuse (opioids, alcohol, nicotine, stimulants, cocaine). Again, although more research has investigated NS and cannabis use, there is no consensus with regards to their link. A few cross-sectional naturalistic FEP studies failed to find an association between cannabis use and NS (Carr et al., 2009; Hadden et al., 2016; Mané et al., 2015) whereas others have indicated that use within the 6 months prior to hospitalization was related to lower NS during admission for FEP patients (Compton et al., 2007). Additionally, a study with an at-risk for psychosis sample showed that increased consumption of cannabis was associated with fewer NS, before a full-blown psychotic episode (Seddon et al., 2016).

Previous research has suggested that those experiencing a FEP may use cannabis to self-medicate (Khantzian, 1997), possibly alleviating some NS such as anhedonia (Gregg et al., 2007; Potvin et al., 2005; Simon et al., 2015), or that higher NS could imply less hedonic capacity which in turn could reduce

drug-seeking (Compton et al., 2007). Another possible explanation is that those with less severe NS use more cannabis due to better functioning, i.e. are more capable of obtaining substances or more prone to substance abuse, as it has been indicated that FEP patients with cannabis abuse disorder show a stronger premorbid social functioning (Carr et al., 2009; Potvin et al., 2005). Nevertheless, there is still paucity of research, especially in FEP and more research is needed to clarify this association (Seddon et al., 2016; Simon et al., 2015).

4.2 Negative symptoms: clinical and functional outcomes

Baseline NS were related to higher possibility of admission to a psychiatric ward, used as a proxy of deterioration or relapse (Addington et al., 2013). Previous studies are in keeping with our findings indicating that high levels of baseline NS are related to poorer clinical outcome (Lang et al., 2013). Furthermore, previous studies generally support our finding that NS were significantly associated with admission one year after FEP (Morgan et al., 2006; Patel et al., 2015; Sipos, 2001), also reporting an associated increased duration of admission (Patel et al., 2015), and earlier relapse (Uçok et al., 2006), although one study did not replicate this finding (Addington et al., 2010).

In this study baseline NS were associated by worse symptoms, as reflected in GAF-s and did not predict symptomatic remission at follow-up, being in accordance with previous 2- (Cesková et al., 2007) and 3-year follow-up FEP studies (Chang et al., 2012a). However, in other studies lower level of NS at baseline have been found to predict remission in first-episode patients after one or two years of treatment (Díaz et al., 2013; Gaebel et al., 2014; Levine and Leucht, 2013; Üçok et al., 2011; Verma et al., 2012) or even 16 years after FEP (Marchesi et al., 2014b, 2015). A possible explanation for the inconsistent findings is that it could mainly be persistent NS that predict follow-up non-remission (Chang et al., 2012a; Edwards et al., 1999; Galderisi et al., 2013; Malla et al., 2004) and prevent patients from reaching a lasting remission state (Gaebel et al., 2014). Possible reasons for that would be their severely impairing and treatment-resistant nature (Üçok and Ergül, 2014), in addition to treatment discontinuation being

more prominent in patients with persistent NS (Galderisi et al., 2013). In this study persistence of NS was not measured, thus we cannot contribute to this hypothesis.

Risk behaviours, i.e. suicidality and violence incidents, were not predicted by NS levels. Our results are consistent with another FEP study that failed to find an association between NS and suicide attempts (Bertelsen et al., 2007). In a recent FEP study, the risk of suicide has been related to an increase in both positive and negative symptoms, thus with an overall escalating symptom severity (Mitter et al., 2013). In a review, Pompili *et al.* (Pompili et al., 2011) indicated that more severe NS could predict suicidality in FEP via a possible increase in insight, which together with persistent reduced functioning and quality of life could increase hopelessness. However, others have suggested that prominent NS and especially expressive deficits could reduce the experience of distress caused by psychosis and thus the feeling of hopelessness is reduced, leading to decreased suicidal behavior (Chang et al., 2014). However, findings on the association between NS and suicidality remains inconsistent (Ventriglio et al., 2016).

Violent incidents at follow-up and NS were not associated, being in agreement with FEP studies that have linked mainly positive (Foley et al., 2007; Winsper et al., 2013) or manic symptoms (Dean et al., 2007; Large and Nielssen, 2011) or no specific symptoms at all (Langeveld et al., 2014) to violent behavior during FEP. Moreover, a recent study has indicated that there are diverse pathways to violent behavior following FEP, influenced by different profiles of premorbid delinquency, that should be taken into account in studies predicting violence in FEP (Winsper et al., 2013).

Higher NS at baseline were also associated with worse functioning at 1-year follow-up as reflected by the GAF-d scores. This finding is consistent with most FEP studies to date that show NS as a critical determinant of both global and social functioning (Cacciotti-Saija et al., 2016) as well as real-world functioning (Robertson et al., 2014), for at least 2 years after the FEP (Bergé et al., 2016). Recent research has supported this link at the at-risk for psychosis stage as well (Meyer et al., 2014). Thus, it could be that those with high negative symptoms at presentation, even when these symptoms decrease,

are less likely to achieve recovery, which could be explained by highly disrupted premorbid functioning (Gee et al., 2016).

4.3 Strengths and limitations

This study has several strengths. The FEP sample was large, naturalistic, from different EIS within well-defined catchment areas, with minimal confounding effects of chronicity, institutionalization and prolonged exposure to antipsychotic treatment. Previous studies have indicated that FEP patients with higher NS might be at greater risk of dropping out (AlAqeel and Margolese, 2012; Thompson et al., 2011; Üçok and Ergül, 2014). Thus, although there was a considerable amount of missing data due to the naturalistic follow-up study design, MI was applied in order to correct for biases due to non-completion (Schafer and Graham, 2002). The differences between the original dataset and the pooled estimates showed that MI took into account the fact that those with missing follow-up data might have had high NS scores.

Nonetheless, a number of caveats need to be considered. Firstly, due to the design of this study, some ethnic minorities and clinical subgroups might have been over/under-represented. Patients of Asian ethnicity were more likely to have completed the PANSS scale at baseline whereas those who identified themselves as “Black Other” ethnicity (i.e. not Black African, Caribbean or British) were less likely to have done so. This limits the generalizability of the findings. Concerning clinical characteristics, patients with lower severity of positive symptoms were more likely to have a fully completed PANSS at baseline, leading to over-representation of cases with lower positive symptoms. However, their mean difference was less than 3 points, possibly not representing a clinically significant difference. Additionally, cross-sectional remission rate estimation at baseline and follow-up tends to be more vulnerable to confounding variables and lacks specificity. Thus, it has been suggested that in longitudinal investigations remission should be examined at six-month intervals (AlAqeel and Margolese, 2012; Gaebel et al., 2014), which was not possible in the current study. Lastly, regarding controlling for secondary NS, although this study

controlled for positive symptoms and depression, it did not take into account extra-pyramidal side-effects (EPS) since there was no measure available (Millan et al., 2014).

6. Clinical implications

The present findings suggest that NS are associated poorer global functioning and symptomatic outcomes and increased likelihood of admission, leading to several clinical implications. This is noteworthy since social and occupational functioning have been indicated as the most important recovery markers by both field experts (Kane et al., 2003) and experts by lived experience (Pitt et al., 2007). Based on the relative fluctuation of NS in FEP and their increasing stability after the first year (Chang et al., 2011; Ventura et al., 2015), this period might be a therapeutic window to ameliorate negative symptomatology, prevent disability and maximize functional outcome. Further investigations should examine the prognostic significance of timely, intensive and integrated intervention in NS during this potential critical period in preventing emergence of persistence. Careful monitoring of those showing higher NS at presentation warrants the attention of EIS,(Gee et al., 2016) if possible from the at-risk stage of the illness when NS often occur (Fusar-Poli et al., 2013). While emphasizing the need for specific treatment approaches for reducing the burden of NS (Schennach-Wolff et al., 2011; Verdoux et al., 2001), it might be important to distinguish between primary NS and secondary NS, as the latter can be subject to treatment changes (Carbon and Correll, 2014).

7. Conclusion

Negative symptoms in FEP are a significant problem, leading to worse functional and clinical outcomes even amongst patients treated by specialist services. Since pharmacological treatments (Fusar-Poli et al., 2015) and psychosocial interventions (Jauhar et al., 2014; Østergaard Christensen et al., 2014) have shown to have little or no effect, further studies are needed in order to tackle NS, early and effectively, maximizing the long-term recovery for FEP patients.

Acknowledgements

Initial pilot work within Camden and Islington EIS was supported by Islington Primary Care Trust. We are extremely grateful to clinicians and patients from the Early Intervention teams participating as part of the MiData Consortium for their time and enthusiasm. We would also like to thank Alexandros Rammos, PhD student at Trinity College, University of Dublin, who assisted on the supervision of statistical analyses for the first draft. This work was supported by the NIHR Biomedical Research Centre for Mental Health at the South London and Maudsley NHS Foundation Trust and Institute of Psychiatry, King's College London.

References

Abdel-Baki, A., Létourneau, G., Morin, C., Ng, A., 2013. Resumption of work or studies after first-episode psychosis: the impact of vocational case management. Early Interv Psychiatry 7, 391–398. doi:10.1111/eip.12021

Addington, D.E., Beck, C., Wang, J., Adams, B., Pryce, C., Zhu, H., Kang, J., McKenzie, E., 2010. Predictors of admission in first-episode psychosis: developing a risk adjustment model for service comparisons. Psychiatr Serv 61, 483–488. doi:10.1176/appi.ps.61.5.483

Addington, D.E., Patten, S.B., McKenzie, E., Addington, J., 2013. Relationship Between Relapse and Hospitalization in First-Episode Psychosis. Psychiatric Services 64, 796–799. doi:10.1176/appi.ps.201200440

Addington, J., Addington, D., 1998. Effect of substance misuse in early psychosis. Br J Psychiatry Suppl 172, 134–136.

AlAqeel, B., Margolese, H.C., 2012. Remission in schizophrenia: critical and systematic review. Harv Rev Psychiatry 20, 281–297. doi:10.3109/10673229.2012.747804

Albert, N., Bertelsen, M., Thorup, A., Petersen, L., Jeppesen, P., Le Quack, P., Krarup, G., Jørgensen, P., Nordentoft, M., 2011. Predictors of recovery from psychosis. Schizophrenia Research 125, 257–266. doi:10.1016/j.schres.2010.10.013

Alvarez-Jimenez, M., Priede, A., Hetrick, S.E., Bendall, S., Killackey, E., Parker, A.G., McGorry, P.D., Gleeson, J.F., 2012. Risk factors for relapse following treatment for first episode psychosis: A systematic review and meta-analysis of longitudinal studies. Schizophrenia Research 139, 116–128. doi:10.1016/j.schres.2012.05.007

Andreasen, N.C., Carpenter, W.T., Kane, J.M., Lasser, R.A., Marder, S.R., Weinberger, D.R., 2005. Remission in schizophrenia: proposed criteria and rationale for consensus. Am J Psychiatry 162, 441–449. doi:10.1176/appi.ajp.162.3.441

Austin, S.F., Mors, O., Secher, R.G., Hjorthøj, C.R., Albert, N., Bertelsen, M., Jensen, H., Jeppesen, P., Petersen, L., Randers, L., Thorup, A., Nordentoft, M., 2013. Predictors of recovery in first episode psychosis: The OPUS cohort at 10year follow-up. Schizophrenia Research 150, 163–168. doi:10.1016/j.schres.2013.07.031

Ayesa-Arriola, R., Manuel Rodríguez-Sánchez, J., Pérez-Iglesias, R., González-Blanch, C., Pardo-García, G., Tabares-Seisdedos, R., Vázquez-Barquero, J.L., Crespo-Facorro, B., 2013. The relevance of cognitive, clinical and premorbid variables in predicting functional outcome for individuals with first-episode psychosis: A 3 year longitudinal study. Psychiatry Research 209, 302–308. doi:10.1016/j.psychres.2013.01.024

Ballageer, T., Malla, A., Manchanda, R., Takhar, J., Haricharan, R., 2005. Is adolescent-onset first-episode psychosis different from adult onset? J Am Acad Child Adolesc Psychiatry 44, 782–789. doi:10.1097/01.chi.0000164591.55942.ea

Bergé, D., Mané, A., Salgado, P., Cortizo, R., Garnier, C., Gomez, L., Diez-Aja, C., Bulbena, A., Pérez, V., 2016. Predictors of Relapse and Functioning in First-Episode Psychosis: A Two-Year Follow-Up Study. Psychiatric Services 67, 227–233. doi:10.1176/appi.ps.201400316

Bertelsen, M., Jeppesen, P., Petersen, L., Thorup, A., Øhlenschlaeger, J., le Quach, P., Christensen, T.Ø., Krarup, G., Jørgensen, P., Nordentoft, M., 2008. Five-year follow-up of a randomized multicenter trial of intensive early intervention vs standard treatment for patients with a first episode of psychotic illness: the OPUS trial. Arch. Gen. Psychiatry 65, 762–771. doi:10.1001/archpsyc.65.7.762

Bertelsen, M., Jeppesen, P., Petersen, L., Thorup, A., OHLENSCHLAeGER, J., Quach, P.L., Christensen, T.O., Krarup, G., Jorgensen, P., Nordentoft, M., 2007. Suicidal behaviour and mortality in first-episode psychosis: the OPUS trial. The British Journal of Psychiatry 191, s140–s146. doi:10.1192/bjp.191.51.s140

Best, M.W., Grossman, M., Oyewumi, L.K., Bowie, C.R., 2014. Examination of the Positive and Negative Syndrome Scale factor structure and longitudinal relationships with functioning in early psychosis: PANSS factor structure and functioning. Early Intervention in Psychiatry n/a-n/a. doi:10.1111/eip.12190

Cacciotti-Saija, C., Langdon, R., Ward, P.B., Hickie, I.B., Guastella, A.J., 2016. Clinical symptoms predict concurrent social and global functioning in an early psychosis sample: Clinical symptoms predict functioning in early psychosis. Early Intervention in Psychiatry n/a-n/a. doi:10.1111/eip.12295

Carbon, M., Correll, C.U., 2014. Thinking and acting beyond the positive: the role of the cognitive and negative symptoms in schizophrenia. CNS Spectrums 19, 35–53. doi:10.1017/S1092852914000601

Carr, J.A.R., Norman, R.G.M., Manchanda, R., 2009. Sociodemographic and clinical characteristics of patients presenting with first-episode psychosis and concurrent substance misuse. Early Intervention in Psychiatry 3, 75–79. doi:10.1111/j.1751-7893.2008.00100.x

Cesková, E., Radovan, P., Tomás, K., Hana, K., 2007. One-year follow-up of patients with first-episode schizophrenia (comparison between remitters and non-remitters). Neuropsychiatr Dis Treat 3, 153–160.

Chang, W.C., Chen, E.S.M., Hui, C.L.M., Chan, S.K.W., Lee, E.H.M., Chen, E.Y.H., 2014. The relationships of suicidal ideation with symptoms, neurocognitive function, and psychological factors in patients with first-episode psychosis. Schizophrenia Research 157, 12–18. doi:10.1016/j.schres.2014.06.009

Chang, W.C., Hui, C.L.M., Tang, J.Y.M., Wong, G.H.Y., Lam, M.M.L., Chan, S.K.W., Chen, E.Y.H., 2011. Persistent negative symptoms in first-episode schizophrenia: a prospective three-year follow-up study. Schizophr. Res. 133, 22–28. doi:10.1016/j.schres.2011.09.006

Chang, W.C., Lau, C.F.C., Chan, S.S.I., Hui, C.L.M., Chan, S.K.W., Lee, E.H.M., Lin, J., Chen, E.Y.H., 2016. Premorbid, clinical and cognitive correlates of primary negative symptoms in first-episode psychosis. Psychiatry Research 242, 144–149. doi:10.1016/j.psychres.2016.05.045

Chang, W.C., Tang, J.Y., Hui, C.L., Lam, M.M., Chan, S.K., Wong, G.H., Chiu, C.P., Chen, E.Y., 2012a. Prediction of remission and recovery in young people presenting with first-episode psychosis in Hong Kong: A 3-year follow-up study. Australian and New Zealand Journal of Psychiatry 46, 100–108. doi:10.1177/0004867411428015

Chang, W.C., Tang, J.Y.M., Hui, C.L.M., Lam, M.M.L., Wong, G.H.Y., Chan, S.K.W., Chiu, C.P.Y., Chung, D.W.S., Law, C.W., Tso, S., Chan, K., Hung, S.F., Chen, E.Y.H., 2012b. Duration of untreated psychosis: Relationship with baseline characteristics and three-year outcome in first-episode psychosis. Psychiatry Research 198, 360–365. doi:10.1016/j.psychres.2011.09.006

Chue, P., Lalonde, J., 2014. Addressing the unmet needs of patients with persistent negative symptoms of schizophrenia: emerging pharmacological treatment options. Neuropsychiatric Disease and Treatment 777. doi:10.2147/NDT.S43404

Compton, M.T., Whicker, N.E., Hochman, K.M., 2007. Alcohol and cannabis use in Urban, African American, first-episode schizophrenia-spectrum patients: associations with positive and negative symptoms. J Clin Psychiatry 68, 1939–1945.

Corcoran, C.M., Kimhy, D., Parrilla-Escobar, M.A., Cressman, V.L., Stanford, A.D., Thompson, J., David, S.B., Crumbley, A., Schobel, S., Moore, H., Malaspina, D., 2011. The relationship of social function to depressive and negative symptoms in individuals at clinical high risk for psychosis. Psychological Medicine 41, 251–261. doi:10.1017/S0033291710000802

Dean, K., Walsh, E., Morgan, C., Demjaha, A., Dazzan, P., Morgan, K., Lloyd, T., Fearon, P., Jones, P.B., Murray, R.M., 2007. Aggressive behaviour at first contact with services: findings from the AESOP First Episode Psychosis Study. Psychological Medicine 37, 547–557. doi:10.1017/S0033291706008920

Díaz, I., Pelayo-Terán, J.M., Pérez-Iglesias, R., Mata, I., Tabarés-Seisdedos, R., Suárez-Pinilla, P., Vázquez-Barquero, J.L., Crespo-Facorro, B., 2013. Predictors of clinical remission following a

first episode of non-affective psychosis: Sociodemographics, premorbid and clinical variables. Psychiatry Research 206, 181–187. doi:10.1016/j.psychres.2012.10.011

Díaz-Caneja, C.M., Pina-Camacho, L., Rodríguez-Quiroga, A., Fraguas, D., Parellada, M., Arango, C., 2015. Predictors of outcome in early-onset psychosis: a systematic review. npj Schizophrenia 1, 14005. doi:10.1038/npjschz.2014.5

Dominguez, M.-G., Saka, M.C., Lieb, R., Wittchen, H.-U., van Os, J., 2010. Early Expression of Negative/Disorganized Symptoms Predicting Psychotic Experiences and Subsequent Clinical Psychosis: A 10-Year Study. American Journal of Psychiatry 167, 1075–1082. doi:10.1176/appi.ajp.2010.09060883

Drake, R.E., Wallach, M.A., 1989. Substance abuse among the chronic mentally ill. Hosp Community Psychiatry 40, 1041–1046.

Drake, R.J., Addington, J., Viswanathan, A.C., Lewis, S.W., Cotter, J., Yung, A.R., Abel, K.M., 2016. How Age and Gender Predict Illness Course in a First-Episode Nonaffective Psychosis Cohort. The Journal of Clinical Psychiatry e283–e289. doi:10.4088/JCP.14m09369

Edwards, J., McGorry, P.D., Waddell, F.M., Harrigan, S.M., 1999. Enduring negative symptoms in first-episode psychosis: comparison of six methods using follow-up data. Schizophrenia Research 40, 147–158. doi:10.1016/S0920-9964(99)00043-2

Endicott, J., Spitzer, R.L., Fleiss, J.L., Cohen, J., 1976. The global assessment scale. A procedure for measuring overall severity of psychiatric disturbance. Arch. Gen. Psychiatry 33, 766–771.

Esterberg, M., Compton, M., 2012. Family history of psychosis negatively impacts age at onset, negative symptoms, and duration of untreated illness and psychosis in first-episode psychosis patients. Psychiatry Research 197, 23–28. doi:10.1016/j.psychres.2012.03.001

Field, A.P., 2009. Discovering statistics using SPSS: (and sex, drugs and rock "n" roll), 3rd ed. ed. SAGE Publications, Los Angeles.

Fisher, H., Theodore, K., Power, P., Chisholm, B., Fuller, J., Marlowe, K., Aitchison, K.J., Tanna, R., Joyce, J., Sacks, M., Craig, T., Johnson, S., 2008. Routine evaluation in first episode psychosis services: feasibility and results from the MiData project. Social Psychiatry and Psychiatric Epidemiology 43, 960–967. doi:10.1007/s00127-008-0386-1

Foley, S.R., Browne, S., Clarke, M., Kinsella, A., Larkin, C., O'Callaghan, E., 2007. Is violence at presentation by patients with first-episode psychosis associated with duration of untreated psychosis? Soc Psychiatry Psychiatr Epidemiol 42, 606–610. doi:10.1007/s00127-007-0217-9

Fraguas, D., del Rey-Mejías, Á., Moreno, C., Castro-Fornieles, J., Graell, M., Otero, S., Gonzalez-Pinto, A., Moreno, D., Baeza, I., Martínez-Cengotitabengoa, M., Arango, C., Parellada, M., 2014. Duration of untreated psychosis predicts functional and clinical outcome in children and adolescents with first-episode psychosis: A 2-year longitudinal study. Schizophrenia Research 152, 130–138. doi:10.1016/j.schres.2013.11.018

Fusar-Poli, P., Borgwardt, S., Bechdolf, A., Addington, J., Riecher-Rössler, A., Schultze-Lutter, F., Keshavan, M., Wood, S., Ruhrmann, S., Seidman, L.J., Valmaggia, L., Cannon, T., Velthorst, E., De Haan, L., Cornblatt, B., Bonoldi, I., Birchwood, M., McGlashan, T., Carpenter, W., McGorry, P., Klosterkötter, J., McGuire, P., Yung, A., 2013. The Psychosis High-Risk State: A Comprehensive State-of-the-Art Review. JAMA Psychiatry 70, 107. doi:10.1001/jamapsychiatry.2013.269

Fusar-Poli, P., Papanastasiou, E., Stahl, D., Rocchetti, M., Carpenter, W., Shergill, S., McGuire, P., 2015. Treatments of Negative Symptoms in Schizophrenia: Meta-Analysis of 168 Randomized Placebo-Controlled Trials. Schizophrenia Bulletin 41, 892–899. doi:10.1093/schbul/sbu170

Gaebel, W., Riesbeck, M., Wölwer, W., Klimke, A., Eickhoff, M., von Wilmsdorff, M., Heuser, I., Maier, W., Klosterkötter, J., Falkai, P., Schlösser, R., Schmitt, A., Riedel, M., Klingberg, S., Köpcke, W., Ohmann, C., Möller, H.-J., 2014. Rates and predictors of remission in first-episode schizophrenia within 1year of antipsychotic maintenance treatment. Results of a randomized controlled trial within the German Research Network on Schizophrenia. Schizophrenia Research 152, 478–486. doi:10.1016/j.schres.2013.04.012

Galderisi, S., Mucci, A., Bitter, I., Libiger, J., Bucci, P., Wolfgang Fleischhacker, W., Kahn, R.S., for the EUFEST Study Group, 2013. Persistent negative symptoms in first episode patients with schizophrenia: Results from the European First Episode Schizophrenia Trial. European Neuropsychopharmacology 23, 196–204. doi:10.1016/j.euroneuro.2012.04.019

Gee, B., Hodgekins, J., Fowler, D., Marshall, M., Everard, L., Lester, H., Jones, P.B., Amos, T., P. Singh, S., Sharma, V., Freemantle, N., Birchwood, M., 2016. The course of negative symptom in first episode psychosis and the relationship with social recovery. Schizophrenia Research 174, 165–171. doi:10.1016/j.schres.2016.04.017

Gregg, L., Barrowclough, C., Haddock, G., 2007. Reasons for increased substance use in psychosis. Clinical Psychology Review 27, 494–510. doi:10.1016/j.cpr.2006.09.004

Hadden, K.L., LeDrew, K., Hogan, K., Thomas, B., 2016. Impact of comorbid cannabis use on outcome in first episode psychosis: Cannabis use in first-episode psychosis. Early Intervention in Psychiatry. doi:10.1111/eip.12377

Hafner, H., Maurer, K., Loffler, W., Riecher-Rossler, A., 1993. The influence of age and sex on the onset and early course of schizophrenia. The British Journal of Psychiatry 162, 80–86. doi:10.1192/bjp.162.1.80

Harvey, P.D., Koren, D., Reichenberg, A., Bowie, C.R., 2006. Negative Symptoms and Cognitive Deficits: What Is the Nature of Their Relationship? Schizophrenia Bulletin 32, 250–258. doi:10.1093/schbul/sbj011

Hunter, R., Barry, S., 2012. Negative symptoms and psychosocial functioning in schizophrenia: Neglected but important targets for treatment. European Psychiatry 27, 432–436. doi:10.1016/j.eurpsy.2011.02.015

Jauhar, S., McKenna, P.J., Radua, J., Fung, E., Salvador, R., Laws, K.R., 2014. Cognitive-behavioural therapy for the symptoms of schizophrenia: systematic review and meta-analysis with examination of potential bias. The British Journal of Psychiatry 204, 20–29. doi:10.1192/bjp.bp.112.116285

Jeppesen, P., Petersen, L., Thorup, A., Abel, M.-B., Øhlenschlaeger, J., Christensen, T.Ø., Krarup, G., Jørgensen, P., Nordentoft, M., 2008. The association between pre-morbid adjustment, duration of untreated psychosis and outcome in first-episode psychosis. Psychol Med 38, 1157–1166. doi:10.1017/S0033291708003449

Kane, J.M., Leucht, S., Carpenter, D., Docherty, J.P., Expert Consensus Panel for Optimizing Pharmacologic Treatment of Psychotic Disorders, 2003. The expert consensus guideline series. Optimizing pharmacologic treatment of psychotic disorders. Introduction: methods, commentary, and summary. J Clin Psychiatry 64 Suppl 12, 5–19.

Kay, S.R., Fiszbein, A., Opler, L.A., 1987. The positive and negative syndrome scale (PANSS) for schizophrenia. Schizophr Bull 13, 261–276.

Kay, S.R., Sevy, S., 1990. Pyramidical Model of Schizophrenia. Schizophrenia Bulletin 16, 537–545. doi:10.1093/schbul/16.3.537

Khantzian, E.J., 1997. The Self-Medication Hypothesis of Substance Use Disorders: A Reconsideration and Recent Applications. Harvard Review of Psychiatry 4, 231–244. doi:10.3109/10673229709030550

Kim, K.R., Song, Y.Y., Park, J.Y., Lee, E.H., Lee, M., Lee, S.Y., Kang, J.I., Lee, E., Yoo, S.W., An, S.K., Kwon, J.S., 2013. The relationship between psychosocial functioning and resilience and negative symptoms in individuals at ultra-high risk for psychosis. Australian & New Zealand Journal of Psychiatry 47, 762–771. doi:10.1177/0004867413488218

Kirkpatrick, B., 2014. Progress in the Study of Negative Symptoms. Schizophrenia Bulletin 40, S101–S106. doi:10.1093/schbul/sbt158

Kjelby, E., Jørgensen, H.A., Kroken, R.A., Løberg, E.-M., Johnsen, E., 2011. Anti-depressive effectiveness of olanzapine, quetiapine, risperidone and ziprasidone: a pragmatic, randomized trial. BMC Psychiatry 11. doi:10.1186/1471-244X-11-145

Köhler, S., van der Werf, M., Hart, B., Morrison, G., McCreadie, R., Kirkpatrick, B., Verkaaik, M., Krabbendam, L., Verhey, F., van Os, J., Allardyce, J., 2009. Evidence that better outcome of psychosis in women is reversed with increasing age of onset: A population-based 5-year follow-up study. Schizophrenia Research 113, 226–232. doi:10.1016/j.schres.2009.05.017

Køster, A., Lajer, M., Lindhardt, A., Rosenbaum, B., 2008. Gender differences in first episode psychosis. Social Psychiatry and Psychiatric Epidemiology 43, 940–946. doi:10.1007/s00127-008-0384-3

Lang, F.U., Kösters, M., Lang, S., Becker, T., Jäger, M., 2013. Psychopathological long-term outcome of schizophrenia - a review. Acta Psychiatrica Scandinavica 127, 173–182. doi:10.1111/acps.12030

Langeveld, J., Bjørkly, S., Auestad, B., Barder, H., Evensen, J., ten Velden Hegelstad, W., Joa, I., Johannessen, J.O., Larsen, T.K., Melle, I., Opjordsmoen, S., Røssberg, J.I., Rund, B.R., Simonsen, E., Vaglum, P., McGlashan, T., Friis, S., 2014. Treatment and violent behavior in persons with first episode psychosis during a 10-year prospective follow-up study. Schizophrenia Research 156, 272–276. doi:10.1016/j.schres.2014.04.010

Large, M.M., Nielssen, O., 2011. Violence in first-episode psychosis: A systematic review and meta-analysis. Schizophrenia Research 125, 209–220. doi:10.1016/j.schres.2010.11.026

Levine, S.Z., Leucht, S., 2013. Attaining and sustaining remission of predominant negative symptoms. Schizophr. Res. 143, 60–64. doi:10.1016/j.schres.2012.11.010

Little, R.J.A., Rubin, D.B., 1991. Statistical Analysis with Missing Data. Journal of Educational Statistics 16, 150. doi:10.2307/1165119

Lyne, J., O'Donoghue, B., Owens, E., Renwick, L., Madigan, K., Kinsella, A., Clarke, M., Turner, N., O'Callaghan, E., 2012. Prevalence of item level negative symptoms in first episode psychosis diagnoses. Schizophr. Res. 135, 128–133. doi:10.1016/j.schres.2012.01.004

Malla, A., 2005. First-Episode Psychosis: Psychopathology, Quality of Life, and Functional Outcome. Schizophrenia Bulletin 31, 650–671. doi:10.1093/schbul/sbi031

Malla, A.K., Norman, R.M.G., Takhar, J., Manchanda, R., Townsend, L., Scholten, D., Haricharan, R., 2004. Can Patients at Risk for Persistent Negative Symptoms Be Identified During Their First Episode of Psychosis?: The Journal of Nervous and Mental Disease 192, 455–463. doi:10.1097/01.nmd.0000131804.34977.c1

Mané, A., Fernández-Expósito, M., Bergé, D., Gómez-Pérez, L., Sabaté, A., Toll, A., Diaz, L., Diez-Aja, C., Perez, V., 2015. Relationship between cannabis and psychosis: Reasons for use and associated clinical variables. Psychiatry Research 229, 70–74. doi:10.1016/j.psychres.2015.07.070

Marchesi, C., Affaticati, A., Monici, A., De Panfilis, C., Ossola, P., Tonna, M., 2015. Severity of core symptoms in first episode schizophrenia and long-term remission. Psychiatry Research 225, 129–132. doi:10.1016/j.psychres.2014.11.005

Marchesi, C., Affaticati, A., Monici, A., De Panfilis, C., Ossola, P., Tonna, M., 2014a. Predictors of symptomatic remission in patients with first-episode schizophrenia: A 16years follow-up study. Comprehensive Psychiatry 55, 778–784. doi:10.1016/j.comppsych.2013.12.011

Marchesi, C., Affaticati, A., Monici, A., De Panfilis, C., Ossola, P., Tonna, M., 2014b. Predictors of symptomatic remission in patients with first-episode schizophrenia: a 16years follow-up study. Compr Psychiatry 55, 778–784. doi:10.1016/j.comppsych.2013.12.011

Meyer, E.C., Carrion, R.E., Cornblatt, B.A., Addington, J., Cadenhead, K.S., Cannon, T.D., McGlashan, T.H., Perkins, D.O., Tsuang, M.T., Walker, E.F., Woods, S.W., Heinssen, R., Seidman, L.J., the NAPLS group, 2014. The Relationship of Neurocognition and Negative Symptoms to Social and Role Functioning Over Time in Individuals at Clinical High Risk in the First Phase of the North American Prodrome Longitudinal Study. Schizophrenia Bulletin 40, 1452–1461. doi:10.1093/schbul/sbt235

Milev, P., Ho, B.-C., Arndt, S., Andreasen, N.C., 2005. Predictive Values of Neurocognition and Negative Symptoms on Functional Outcome in Schizophrenia: A Longitudinal First-Episode Study With 7-Year Follow-Up. American Journal of Psychiatry 162, 495–506. doi:10.1176/appi.ajp.162.3.495

Millan, M.J., Fone, K., Steckler, T., Horan, W.P., 2014. Negative symptoms of schizophrenia: Clinical characteristics, pathophysiological substrates, experimental models and prospects for improved treatment. European Neuropsychopharmacology 24, 645–692. doi:10.1016/j.euroneuro.2014.03.008

Mitter, N., Subramaniam, M., Abdin, E., Poon, L.Y., Verma, S., 2013. Predictors of suicide in Asian patients with first episode psychosis. Schizophrenia Research 151, 274–278. doi:10.1016/j.schres.2013.10.006

Morgan, V., Korten, A., Jablensky, A., 2006. Modifiable risk factors for hospitalization among people with psychosis: evidence from the National Study of Low Prevalence (Psychotic) Disorders. Australian and New Zealand Journal of Psychiatry 40, 683–690. doi:10.1080/j.1440-1614.2006.01868.x

Norman, R.M.G., Malla, A.K., Manchanda, R., Harricharan, R., Takhar, J., Northcott, S., 2005. Social support and three-year symptom and admission outcomes for first episode psychosis. Schizophrenia Research 80, 227–234. doi:10.1016/j.schres.2005.05.006

Norman, R.M.G., Windell, D., Manchanda, R., Harricharan, R., Northcott, S., 2012. Social support and functional outcomes in an early intervention program. Schizophrenia Research 140, 37–40. doi:10.1016/j.schres.2012.07.003

Novick, D., Haro, J.M., Suarez, D., Vieta, E., Naber, D., 2009. Recovery in the outpatient setting: 36-month results from the Schizophrenia Outpatients Health Outcomes (SOHO) study. Schizophr. Res. 108, 223–230. doi:10.1016/j.schres.2008.11.007

Ochoa, S., Usall, J., Cobo, J., Labad, X., Kulkarni, J., 2012. Gender Differences in Schizophrenia and First-Episode Psychosis: A Comprehensive Literature Review. Schizophrenia Research and Treatment 2012, 1–9. doi:10.1155/2012/916198

Østergaard Christensen, T., Vesterager, L., Krarup, G., Olsen, B.B., Melau, M., Gluud, C., Nordentoft, M., 2014. Cognitive remediation combined with an early intervention service in first episode psychosis. Acta Psychiatr Scand 130, 300–310. doi:10.1111/acps.12287

Patel, R., Jayatilleke, N., Broadbent, M., Chang, C.-K., Foskett, N., Gorrell, G., Hayes, R.D., Jackson, R., Johnston, C., Shetty, H., Roberts, A., McGuire, P., Stewart, R., 2015. Negative symptoms in schizophrenia: a study in a large clinical sample of patients using a novel automated method. BMJ Open 5, e007619. doi:10.1136/bmjopen-2015-007619

Petersen, L., Thorup, A., Øqhlenschlaeger, J., Christensen, T.Ø., Jeppesen, P., Krarup, G., Jørrgensen, P., Mortensen, E.L., Nordentoft, M., 2008. Predictors of remission and recovery in a first-episode schizophrenia spectrum disorder sample: 2-year follow-up of the OPUS trial. Can J Psychiatry 53, 660–670.

Pitt, L., Kilbride, M., Nothard, S., Welford, M., Morrison, A.P., 2007. Researching recovery from psychosis: a user-led project. Psychiatric Bulletin 31, 55–60. doi:10.1192/pb.bp.105.008532

Pompili, M., Serafini, G., Innamorati, M., Lester, D., Shrivastava, A., Girardi, P., Nordentoft, M., 2011. Suicide risk in first episode psychosis: A selective review of the current literature. Schizophrenia Research 129, 1–11. doi:10.1016/j.schres.2011.03.008

Potvin, S., Sepehry, A.A., Stip, E., 2005. A meta-analysis of negative symptoms in dual diagnosis schizophrenia. Psychological Medicine 36, 431. doi:10.1017/S003329170500574X

Rabinowitz, J., Levine, S.Z., Garibaldi, G., Bugarski-Kirola, D., Berardo, C.G., Kapur, S., 2012. Negative symptoms have greater impact on functioning than positive symptoms in schizophrenia: Analysis of CATIE data. Schizophrenia Research 137, 147–150. doi:10.1016/j.schres.2012.01.015

Rietschel, L., Lambert, M., Karow, A., Zink, M., Müller, H., Heinz, A., de Millas, W., Janssen, B., Gaebel, W., Schneider, F., Naber, D., Juckel, G., Krüger-Özgürdal, S., Wobrock, T., Wagner, M., Maier, W., Klosterkötter, J., Bechdolf, A., PREVENT study group, 2015. Clinical high risk for psychosis: gender differences in symptoms and social functioning: Gender differences in HR for psychosis. Early Intervention in Psychiatry n/a-n/a. doi:10.1111/eip.12240

Robertson, B.R., Prestia, D., Twamley, E.W., Patterson, T.L., Bowie, C.R., Harvey, P.D., 2014. Social competence versus negative symptoms as predictors of real world social functioning in schizophrenia. Schizophrenia Research 160, 136–141. doi:10.1016/j.schres.2014.10.037

Schafer, J.L., Graham, J.W., 2002. Missing data: our view of the state of the art. Psychol Methods 7, 147–177.

Schennach-Wolff, R., Jäger, M., Mayr, A., Meyer, S., Kühn, K.-U., Klingberg, S., Heuser, I., Klosterkötter, J., Gastpar, M., Schmitt, A., Schlösser, R., Schneider, F., Gaebel, W., Seemüller, F., Möller, H.-J., Riedel, M., 2011. Predictors of response and remission in the acute treatment of first-episode schizophrenia patients — Is it all about early response? European Neuropsychopharmacology 21, 370–378. doi:10.1016/j.euroneuro.2010.10.003

Schubert, K.O., Clark, S.R., Baune, B.T., 2015. The use of clinical and biological characteristics to predict outcome following First Episode Psychosis. Australian & New Zealand Journal of Psychiatry 49, 24–35. doi:10.1177/0004867414560650

Schultz, S.K., Miller, D.D., Oliver, S.E., Arndt, S., Flaum, M., Andreasen, N.C., 1997. The life course of schizophrenia: age and symptom dimensions. Schizophr. Res. 23, 15–23. doi:10.1016/S0920-9964(96)00087-4

Seddon, J.L., Birchwood, M., Copello, A., Everard, L., Jones, P.B., Fowler, D., Amos, T., Freemantle, N., Sharma, V., Marshall, M., Singh, S.P., 2016. Cannabis Use Is Associated With Increased Psychotic Symptoms and Poorer Psychosocial Functioning in First-Episode Psychosis: A Report From the UK National EDEN Study. Schizophrenia Bulletin 42, 619–625. doi:10.1093/schbul/sbv154

Sevy, S., Robinson, D.G., Holloway, S., Alvir, J.M., Woerner, M.G., Bilder, R., Goldman, R., Lieberman, J., Kane, J., 2008. Correlates of substance misuse in patients with first-episode schizophrenia and schizoaffective disorder: Substance misuse in schizophrenia. Acta Psychiatrica Scandinavica 104, 367–374. doi:10.1111/j.1600-0447.2001.00452.x

Simon, N., Belzeaux, R., Adida, M., Azorin, J.-M., 2015. Symptômes négatifs dans la schizophrénie et addiction. L'Encéphale 41, 6S27-6S31. doi:10.1016/S0013-7006(16)30007-0

Singh, S.P., 2010. Early intervention in psychosis. Br J Psychiatry 196, 343–345. doi:10.1192/bjp.bp.109.075804

Singh, S.P., 2000. Three-year outcome of first-episode psychoses in an established community psychiatric service. The British Journal of Psychiatry 176, 210–216. doi:10.1192/bjp.176.3.210

Singh, S.P., Cooper, J.E., Fisher, H.L., Tarrant, C.J., Lloyd, T., Banjo, J., Corfe, S., Jones, P., 2005. Determining the chronology and components of psychosis onset: The Nottingham Onset Schedule (NOS). Schizophrenia Research 80, 117–130. doi:10.1016/j.schres.2005.04.018

Sipos, A., 2001. Patterns and predictors of hospitalisation in first-episode psychosis: Prospective cohort study. The British Journal of Psychiatry 178, 518–523. doi:10.1192/bjp.178.6.518

Stone, J.M., Fisher, H.L., Major, B., Chisholm, B., Woolley, J., Lawrence, J., Rahaman, N., Joyce, J., Hinton, M., Johnson, S., Young, A.H., 2014. Cannabis use and first-episode psychosis: relationship with manic and psychotic symptoms, and with age at presentation. Psychological Medicine 44, 499–506. doi:10.1017/S0033291713000883

Tait, L., Birchwood, M., Trower, P., 2002. A new scale (SES) to measure engagement with community mental health services. Journal of Mental Health 11, 191–198. doi:10.1080/09638230020023570-2

Tandberg, M., Ueland, T., Andreassen, O.A., Sundet, K., Melle, I., 2012. Factors associated with occupational and academic status in patients with first-episode psychosis with a particular focus on neurocognition. Soc Psychiatry Psychiatr Epidemiol 47, 1763–1773. doi:10.1007/s00127-012-0477-x

Tang, J.Y.-M., Chang, W.-C., Hui, C.L.-M., Wong, G.H.-Y., Chan, S.K.-W., Lee, E.H.-M., Yeung, W.-S., Wong, C.-K., Tang, W.-N., Chan, W.-F., Pang, E.P.-F., Tso, S., Ng, R.M.-K., Hung, S.-F., Dunn, E.L.-W., Sham, P.-C., Chen, E.Y.-H., 2014. Prospective relationship between duration of

untreated psychosis and 13-year clinical outcome: A first-episode psychosis study. Schizophrenia Research 153, 1–8. doi:10.1016/j.schres.2014.01.022

Tarricone, I., Boydell, J., Panigada, S., Allegri, F., Marcacci, T., Minenna, M.G., Kokona, A., Triolo, F., Storbini, V., Michetti, R., Morgan, C., Di Forti, M., Murray, R.M., Berardi, D., 2014. The impact of substance use at psychosis onset on First Episode Psychosis course: Results from a 1 year follow-up study in Bologna. Schizophrenia Research 153, 60–63. doi:10.1016/j.schres.2014.01.014

Thompson, J., Berk, M., Dean, O., Kohlmann, K., Jeavons, S., Bush, A., Copolov, D., 2011. Who's left? Symptoms of schizophrenia that predict clinical trial dropout. Hum Psychopharmacol 26, 609–613. doi:10.1002/hup.1253

Thorup, A., Albert, N., Bertelsen, M., Petersen, L., Jeppesen, P., Le Quack, P., Krarup, G., Jørgensen, P., Nordentoft, M., 2014. Gender differences in first-episode psychosis at 5-year follow-up – two different courses of disease? Results from the OPUS study at 5-year follow-up. European Psychiatry 29, 44–51. doi:10.1016/j.eurpsy.2012.11.005

Thorup, A., Petersen, L., Jeppesen, P., Ohlenschlaeger, J., Christensen, T., Krarup, G., Jorgensen, P., Nordentoft, M., 2007. Gender differences in young adults with first-episode schizophrenia spectrum disorders at baseline in the Danish OPUS study. J. Nerv. Ment. Dis. 195, 396–405. doi:10.1097/01.nmd.0000253784.59708.dd

Tseliou, F., Johnson, S., Major, B., Rahaman, N., Joyce, J., Lawrence, J., Mann, F., Tapfumaneyi, A., Chisholm, B., Chamberlain-Kent, N., Hinton, M.F., Fisher, H.L., MiData Consortium, 2015. Gender differences in one-year outcomes of first-presentation psychosis patients in inner-city UK Early Intervention Services: 1-year outcomes of EI services by gender. Early Intervention in Psychiatry n/a-n/a. doi:10.1111/eip.12235

Üçok, A., Ergül, C., 2014. Persistent negative symptoms after first episode schizophrenia: A 2-year follow-up study. Schizophr. Res. 158, 241–246. doi:10.1016/j.schres.2014.07.021

Uçok, A., Polat, A., Cakir, S., Genç, A., 2006. One year outcome in first episode schizophrenia. Predictors of relapse. Eur Arch Psychiatry Clin Neurosci 256, 37–43. doi:10.1007/s00406-005-0598-2

Üçok, A., Serbest, S., Kandemir, P.E., 2011. Remission after first-episode schizophrenia: Results of a long-term follow-up. Psychiatry Research 189, 33–37. doi:10.1016/j.psychres.2010.11.013

van der Ven, E., Bourque, F., Joober, R., Selten, J.-P., Malla, A.K., 2012. Comparing the clinical presentation of first-episode psychosis across different migrant and ethnic minority groups in Montreal, Quebec. Can J Psychiatry 57, 300–308.

Veling, W., 2013. Ethnic minority position and risk for psychotic disorders. Curr Opin Psychiatry 26, 166–171. doi:10.1097/YCO.0b013e32835d9e43

Ventriglio, A., Gentile, A., Bonfitto, I., Stella, E., Mari, M., Steardo, L., Bellomo, A., 2016. Suicide in the Early Stage of Schizophrenia. Frontiers in Psychiatry 7. doi:10.3389/fpsyt.2016.00116

Ventura, J., Subotnik, K.L., Gitlin, M.J., Gretchen-Doorly, D., Ered, A., Villa, K.F., Hellemann, G.S., Nuechterlein, K.H., 2015. Negative symptoms and functioning during the first year after a recent onset of schizophrenia and 8years later. Schizophrenia Research 161, 407–413. doi:10.1016/j.schres.2014.10.043

Verdoux, H., Liraud, F., Gonzales, B., Assens, F., Abalan, F., van Os, J., 2001. Predictors and outcome characteristics associated with suicidal behaviour in early psychosis: a two-year follow-up of first-admitted subjects. Acta Psychiatrica Scandinavica 103, 347–354. doi:10.1034/j.1600-0447.2001.00202.x

Verma, S., Subramaniam, M., Abdin, E., Poon, L.Y., Chong, S.A., 2012. Symptomatic and functional remission in patients with first-episode psychosis: Remission in first-episode psychosis. Acta Psychiatrica Scandinavica 126, 282–289. doi:10.1111/j.1600-0447.2012.01883.x

White, I.R., Royston, P., Wood, A.M., 2011. Multiple imputation using chained equations: Issues and guidance for practice. Statistics in Medicine 30, 377–399. doi:10.1002/sim.4067

Willhite, R.K., Niendam, T.A., Bearden, C.E., Zinberg, J., O'Brien, M.P., Cannon, T.D., 2008. Gender differences in symptoms, functioning and social support in patients at ultra-high risk for developing a psychotic disorder. Schizophrenia Research 104, 237–245. doi:10.1016/j.schres.2008.05.019

Winsper, C., Singh, S.P., Marwaha, S., Amos, T., Lester, H., Everard, L., Jones, P., Fowler, D., Marshall, M., Lewis, S., Sharma, V., Freemantle, N., Birchwood, M., 2013. Pathways to Violent Behavior During First-Episode Psychosis: A Report From the UK National EDEN Study. JAMA Psychiatry 70, 1287. doi:10.1001/jamapsychiatry.2013.2445

World Health Organization (Ed.), 1993. The ICD-10 classification of mental and behavioural disorders: diagnostic criteria for research. World Health Organization, Geneva.